American Journal of
Biomedical Science & Research

www.biomedgrid.com
ISSN: 2642-1747

Research Article

Progress in the Treatment of Membranous Neuropathy with Integrated Traditional Chinese and Western Medicine

Sun Yu[1] and Dapeng Wang[2]*

[1]*Institute (College) of Integrative Medicine, Dalian Medical University, China*

[2]*Department of Nephrology, The First Affiliated Hospital of Dalian Medical University, China*

***Corresponding author:** Da Peng Wang, Department of Nephrology, The First Affiliated Hospital of Dalian Medical University, 222 Zhongshan Road, Xigang District, Dalian, Liaoning, China.

To Cite This Article: *Sun Yu and Dapeng Wang*. Progress in the Treatment of Membranous Neuropathy with Integrated Traditional Chinese and Western Medicine. Am J Biomed Sci & Res. 2023 20(6) AJBSR.MS.ID.002782,* DOI: 10.34297/AJBSR.2023.20.002782

Received: December 18, 2023; **Published:** December 22, 2023

Abstract

Membranous Nephropathy (MN), also known as membranous glomerulonephritis, can occur at all ages, and can be divided into Idiopathic Membranous Nephropathy (IMN) and Secondary Membranous Nephropathy (SMN). Its incidence rate is increasing year by year. However, there is still significant controversy regarding the treatment of MN, and there is no unified treatment plan for clinical application. Therefore, this article reviews the clinical treatment progress of MN from the perspective of its pathogenesis and treatment.

Keywords: Membranous nephropathy, Primary membranous nephropathy, Secondary membranous nephropathy; Rituximab

Introduction

MN is one of the main causes of adult nephrotic syndrome. About 20% of the patients are Secondary Membranous Nephropathy (SMN), which is mostly related to drug treatment, such as non-steroidal anti-inflammatory drugs, or diseases secondary to malignant tumors, systemic lupus erythematosus, hepatitis B, hepatitis C, and other diseases. The other patients, with unknown etiology, are Idiopathic Membranous Nephropathy (IMN) [1-3]. About one-third of patients with this disease can experience spontaneous remission without treatment, while the remaining patients will maintain proteinuria symptoms and retain renal function for a long time after treatment. But still one-third of patients will progress to end-stage renal disease, and even die.

Research on the Pathogenesis

The main feature of MN is the deposition of immune complexes formed by target antigens and antibodies on the basement membrane, leading to thickening of the glomerular capillary wall. Immuno deposition includes immunoglobulin G, related antigens, and complement components.

Complement Components

Research has shown that the pathogenesis of IMN is the combination of Immunoglobulin G (IgG) antibodies and intrinsic antigens on the basal membrane of podocytes to form a membrane attack complex, leading to podocyte damage. The main type of immune complex in IMN is IgG4, so the key to its pathogenesis lies in the pathway and/or Mannose Binding Lectin (MBL) pathway. In recent years, continuous research has shown that MBL can activate the MBL pathway by binding to IgG4 anti PLA2R antibodies with galactose deficient side chains [4]. In IMN patients with complete MBL deficiency, the complement system can be activated through a bypass pathway [5].

Antigen and Antibody Components

Target Antigen: ① Neutral Endopeptidase (NEP). According

to a foreign case of allogeneic prenatal membranous nephropathy, if the mother lacks NEP in her body, anti NEP antigen antibodies may be produced during early miscarriage or after miscarriage, and then an immune response can be produced through the combination of the placenta and fetal foot cell antigens to cause the disease. The severity of neonatal kidney disease also depends on the severity of the reaction [6] M-type Phospholipase A2 Receptor (PLA2R1). PLA2R is distributed on the glomerular podocyte membrane, and IMN patients contain IgG antibodies that react with PLA2R protein and may lead to podocyte damage and proteinuria [7] Thrombospondin type-1 domain containing 7A (THSD7A). Experiments have shown that 2.5-5% of IMN patients have anti THSD7A antibodies distributed within glomerular podocytes, and the pathogenesis is related to the formation of immune complexes with THSD7A antigen [8]. The antibody titer level is also correlated with the prognosis of MN [9] Exotoxin 1/Exotoxin 2. Research has found that EXT1/EXT2 can be target antigens for SMN, and renal biopsy shows that about 85% of patients have SMN features related to autoimmune diseases, especially lupus disease, and the majority of patients are young women [10] Neuro epidermal growth factor like 1 protein (NELL-1). *Sethi, et al.* found that MN associated with NELL1 has a unique feature, that is, IgG capillary ring staining is segmental or incomplete under immunofluorescence detection [11].

Compared with other antigen related MNs, MNs associated with NELL1 are more significantly associated with malignant tumors [12] Semaphorin 3B (SEMA3B). Immunohistochemistry of the glomeruli of MN patients showed that Sema3B is a novel target antigen for MN, and among the 11 cases of SEMA3B related MN, 8 were children. From this, it can be seen that MN associated with SEMA3B is a unique type, and the affected population is mostly children [13] Neural Cell Adhesion Molecule 1 (NCAM1). Research has found that MCAM1 can be detected and localized in the deposition of glomerular immune complexes, and its reactivity to NCAM1 recombinant protein is also shown in the serum of MN patients associated with NCAM1. Therefore, it can be determined that NCAM1 is a target autoantigen for patients with membranous lupus nephritis [14] Protocadherin 7 (PCDH7). Research has found that PCDH7 and circulating anti PCDH7 autoantibodies are present in PLA2R⑧ Protocadherin 7 (PCDH7). Research has found that PCDH7 and circulating anti PCDH7 autoantibodies are novel antigens in PLA2R negative MN patients [15] Serine protease 1 (HTRA1). HTRA1 has been confirmed to be a unique foot cell antigen of some IMNs, and antibody levels are associated with disease activity [16].

Exogenous antigen: Cationic Bovine Serum Albumin (BSA) is mainly derived from milk and is an exogenous food antigen. In 2011, Debiec and other scholars discovered that circulating BSA and anti BSA antibodies can be detected simultaneously in some children with MN. And the only way for these tested children to obtain this protein in their bodies is through milk, which suggests that exogenous food antigens induce immune responses [17]. Circulating antigens: human foot cell cytoplasmic antigen Aldose Reductase (AR), superoxide dismutase (Manganese superoxide dismutase, SOD2) α- Alpha enolase (ENO1) is located in the cytoplasm of podocytes. *Bruschi, et al.* have shown through research that ENO1 is present in the glomeruli of MN patients, and circulating ENO1 autoantibodies can also be detected in the serum of a large number of MN patients [18]. *Prunotto, et al.,* found that AR and SOD2 are newly expressed proteins in the glomeruli of MN, which can be recognized by corresponding circulating antibodies and detected in subcutaneous immune deposition of the glomeruli [19], indicating that these antigens may be specific to MN.

Treatment Progress

Western Medicine Treatment

At present, the treatment of IMN mainly focuses on PLA2R related treatments. Initially, routine drug support is given based on the patient's complaint and complications, and then immunosuppressive agents are used for treatment. The treatment of SMN patients should be considered from the perspective of potential causes. For SMN patients who have not shown significant improvement after treatment, the treatment approach of IMN patients should be adopted. The treatment plan is as follows:

Symptomatic Treatment: All MN patients should receive symptomatic supportive treatment in the early stages of the disease. For edema symptoms, a low sodium diet should be recommended in daily care, and diuretics should be used in combination with serum electrolyte levels and adverse drug reactions during treatment [20]. After controlling sodium levels, blood pressure can be kept within the normal range. Angiotensin converting enzyme inhibitors and/or angiotensin II receptor antagonists can be used, while also reducing the patient's urine protein and promoting spontaneous symptom relief.

Immunosuppressive Therapy:

a) In 1998, *Ponticelli, et al.* found through a 10-year follow-up study that alternating the use of methylprednisolone and phenylbutyrate nitrogen mustard for 6 months resulted in a higher complete or partial remission rate of nephrotic syndrome and significantly prolonged end-stage renal survival. And therefore, a 6-month course of alternating use of methylprednisolone and phenylbutyrate nitrogen mustard immunosuppressive therapy ("Ponticelli regimen") was established as the standard for treating MN [21].

b) According to the KDIGO guidelines, CNIs+glucocorticoids are recommended for individuals who resist initial treatment regimens based on alkylating agents/hormones. Common CHI drugs include Tacrolimus (TAC) and Cyclosporin (CsA). Research has shown that TAC combined with corticosteroids can effectively alleviate the condition, reduce serum albumin levels, and accelerate disease recovery [22]. CsA can reduce proteinuria concentration in patients with progressive renal failure and delay the rate of renal failure [23].

c) Mycophenolate Mofetil (MMF) is a highly selective immunosuppressive agent that selectively inhibits the proliferation of T and B lymphocytes. Currently, it has been clinically used as a cytotoxic drug or alternative to CNIs for the treatment of IMN

patients. Experimental analysis shows that the efficacy of MMF and CsA combined with low-dose corticosteroids in the treatment of IMN is similar [24].

d) In 2002, *Remuzzi, et al.,* first applied Rituximab (RTX) to the treatment of IMN patients with monoclonal antibodies against CD20. The therapeutic effect was significant, significantly reducing proteinuria levels and thus alleviating the condition [25]. Its therapeutic effect and short-term adverse reactions in IMN patients are superior to traditional immunosuppressive drugs. Anti CD20 antibodies, especially RTX, have gradually become the first-line treatment plan in clinical practice [26]. Rituximab is a human IgG1 type anti-CD20 monoclonal antibody drug. A study reported that a patient with refractory PLA2R related MN in a foreign country was resistant to RTX treatment and had severe adverse reactions. After receiving Rituximab treatment, the condition was effectively relieved, and only mild adverse reactions were observed. The adverse reactions can also quickly disappear after interruption of infusion and/or steroid administration [27] . Obinuzumab is a humanized and glycoengineered monoclonal antibody drug against CD20. Compared with RTX, it has stronger in vitro B cell toxicity, targeting different epitopes on CD20 and causing greater B cell apoptosis [28]. In a follow-up study of 10 MN patients by *Sethi, et al.*, it was found that after 6 months of Obinutuzumab treatment, 4 patients achieved complete remission, 5 patients achieved partial remission, and 1 patient, although not relieved, had a nearly 50% decrease in urinary protein levels. After 12 months of treatment, all patients achieved complete or partial remission and remained in remission until 24 months [29].

Obinutuzumab is undoubtedly a very attractive alternative therapy for RTX resistant or sensitized patients, but we still need to conduct extensive prospective studies to confirm it. Ocrelizumab is a humanized anti-CD20 monoclonal antibody that has been approved for the treatment of Multiple Sclerosis (MS) [30]. A male patient from a foreign country was first diagnosed with MS, followed by clinical manifestations such as edema, massive proteinuria, and hypoalbuminemia, and was diagnosed with PLA2R related MN. Therefore, Ocrelizumab was chosen clinically to avoid double suppression of the immune system and can treat both MS and MN simultaneously. After 12 months of treatment, partial relief was achieved. After 20 months, PLA2R antibodies completely disappeared from circulation, and urine protein concentration decreased to a low level. After 2 years of treatment, the patient's MS and MN did not recur, PLA2R antibodies remained negative, and no significant adverse reactions occurred [31].

Traditional Chinese Medicine Treatment

In traditional Chinese medicine, MN, especially IMN, mainly belongs to the categories of "edema", "turbid urine", "lower back pain", "deficiency and fatigue", etc. Based on a data analysis, MN is mostly a syndrome of deficiency and excess, with spleen and kidney deficiency as the basis and wind, dampness, heat, and blood stasis as the criteria. Among them, stasis and internal obstruction are the most common [32-37]. Therefore, the treatment principle should mainly focus on supporting the right and eliminating evil and treat according to syndrome differentiation.

Diagnosis and Treatment Based on Syndrome Differentiation: Professor *Huang Wenzheng, et al.,* believes that the treatment for spleen and kidney qi deficiency is to strengthen the spleen and benefit the kidneys, and the formula is modified with *Shen Qi Di Huang Tang*; The treatment for spleen kidney yang deficiency is to warm the kidney and strengthen the spleen, and the formula is modified with *Jin Kui Shen Qi Wan*; The treatment of liver and kidney yin deficiency syndrome is to nourish the liver and kidney, clear heat and nourish yin, and use *Zhibai Dihuang* Tang combined with *Zishui Qinggan* Yin with modifications; The treatment of water dampness syndrome involves warming yang and transforming qi, promoting diuresis and reducing swelling. The formula is modified with *Fangji Huangqi Tang* and *Linggui Zhugan Tang*; The treatment of blood stasis syndrome is to nourish blood and promote blood circulation, break through blood and remove stasis. The formula is modified with *Siwu Tang* combined with *Dahuang Buchong* Wan; The syndrome belongs to spleen and kidney deficiency, with a combination of water dampness and blood stasis. The treatment is to strengthen the spleen and kidney, dispel wind and dampness, promote blood circulation and remove blood stasis. The formula is modified with Cicada Silkworm Kidney Wind Decoction.

Professor *Zhan Yongli, et al.,* believes that for patients with lung qi deficiency and blood stasis and water stagnation syndrome, the treatment should be beneficial to the lungs, consolidate the surface, promote blood circulation and diuresis, and choose *Fangji Huangqi* Tang combined with *Danggui Shaoyao* San for treatment; If the syndrome belongs to deficiency of spleen yang and cessation of blood stasis and water, the treatment should be to strengthen the spleen and warm yang, promote blood circulation and diuresis, and choose the combination of solid spleen drink and tonifying yang and restoring five decoction; For patients with kidney yang deficiency and stagnation of blood stasis and water syndrome, the treatment should be warming the kidney to assist yang, promoting blood circulation and promoting diuresis. *Zhenwu Tang* combined with *Taohong Siwu* Tang with modified Chinese herbal medicine should be selected for treatment. Professor *Liu Yuning, et al.* classified MN into four types based on syndrome differentiation: stasis and water obstruction type, treating when resolving phlegm and diuresis, promoting blood circulation and eliminating blood stasis, and selecting *Guizhi* Fuling Pills with modifications; The internal type of dampness and heat should focus on clearing and promoting dampness and heat, clearing the three jiao, and selecting *Sanren Tang*; The liver depression and qi stagnation type should pay attention to soothing the liver and regulating qi, and choose *Chaihu Shugan San* with modifications; Spleen and kidney qi deficiency type is treated by tonifying the spleen and kidney, promoting diuresis and removing blood stasis, and selecting modified *Yiqi Bushen Tang* for treatment. *Yu Dongrong, et al.,* divided MN into two types: the spleen

and kidney qi (yang) deficiency type was treated with tonifying qi, strengthening spleen and warming kidney drugs, and raw astragalus, Codonopsis pilosula, Atractylodes macrocephala, Poria cocos, prepared aconite, Xianling spleen, dodder seed, etc; Qi and Yin deficiency type should be treated with Qi tonifying and Yin nourishing drugs, such as *Taizi Shen*, *Zhimu, Shengdi*, Ligustrum lucidum, Arid lotus root, and Baimao root.

Staged Treatment: Professor Chen Yiping divided MN into two types of syndromes based on different stages of the disease: spleen deficiency and damp heat syndrome was treated with Qingre Membrane Kidney Granule, with the main drugs being Codonopsis pilosula, Atractylodes macrocephala, Salvia miltiorrhiza, Angelica sinensis, Motherwort, Hedyotis diffusa, Scutellaria baicalensis, Shiwei, Plantago asiatica, and Atractylodes macrocephala; Spleen and kidney yang deficiency type should be treated with tonifying kidney membrane kidney granules. The drug composition includes Astragalus membranaceus, Codonopsis pilosula, Atractylodes macrocephala, Yam yam, Yiyanglei, Cistanche deserticola, Red dates, Coix seed, Atractylodes macrocephala, Danshen, and Leonurus heterophyllus. Professor *Lv Renhe, et al.,* divided MN into edema phase, urine turbidity phase, and renal failure phase based on the progression of the disease and treated them in stages. The edema phase was treated using the diuretic method, while the urine turbidity phase was treated from different perspectives of spleen and kidney, wind, and dampness. In the early stage of renal failure, the spleen and kidney should be treated together to support the right and eliminate evil. If the condition persists, it should be cleared and supplemented to provide a way out for evil and protect stomach qi [38]. The pathological staging of membranous nephropathy in stages I and I-II is mostly in the early stage of disease development.

Professor *Wang Yaoguang*, et al., believes that the traditional Chinese medicine syndrome differentiation is more common in the spleen kidney qi deficiency syndrome. Therefore, in the treatment, a combination of tonifying spleen qi and promoting blood circulation and diuresis drugs is often used; Phase II is more common in cases of spleen and kidney yang deficiency and blood stasis. Treatment mainly involves tonifying the spleen and kidney, strengthening the kidney and astringent essence, and promoting blood circulation and diuresis, with the addition of blood breaking and stasis removing drugs as appropriate. Stages III and IV are mostly characterized by the combination of blood stasis and water. Therefore, drugs for tonifying the spleen, tonifying the kidney, resolving blood stasis, and promoting water retention are selected, and insect and ant search drugs may be added as appropriate [39].

In summary, with the deepening understanding of MN in modern medicine, significant progress has been made in pathogenesis. However, it is still worth our continuous research on how to choose treatment plans more accurately and effectively in terms of treatment. At present, clinical treatment focuses on two aspects: basic supportive therapy and immunosuppressive therapy. In immunosuppressive therapy, the therapeutic status of CTX and CNIs is still very stable, and the advantages of RTX are gradually emerging, but still need to be studied in large samples. In addition, the advantages of traditional Chinese medicine in treating MN have been continuously revealed, but a large amount of basic experimental research is still needed to prove it. In the future, we should focus on developing more personalized and targeted treatment plans to improve efficacy, reduce adverse reactions, and improve patient quality of life.

Acknowledgements

None.

Conflict of Interest

None.

References

1. RONCO P, DEBIEC H (2021) Membranous nephropathy: current understanding of various causes in light of new target antigens. Curr Opin Nephrol Hypertens 30(3): 287-293.s
2. Song Ren, Ying Wang, Li Xian, Tadashi Toyama, Meg Jardine, et al. (2017) Comparative effectiveness and tolerance of immunosuppressive treatments for idiopathic membranous nephropathy: A network meta-analysis. PLoS One 12(9): e0184398.
3. Pierre Ronco, Laurence Beck, Hanna Debiec, Fernando C Fervenza, Fan Fan Hou, et al. (2021) Membranous nephropathy. Nat Rev Dis Primers 7(1): 69.
4. BECK LH (2012) Monoclonal anti-PLA2R and recurrent membranous nephropathy: another piece of the puzzle. J Am Soc Nephrol 23(12): 1911-1913.
5. Stéphane Bally, Hanna Debiec, Denise Ponard, Frédérique Dijoud, John Rendu, et al. (2016) Phospholipase A2 Receptor-Related Membranous Nephropathy and Mannan-Binding Lectin Deficiency. J Am Soc Nephrol 27(12): 3539-3544.
6. Hanna Debiec, Jeroen Nauta, Florence Coulet, Mirjam van der Burg, Vincent Guigonis, et al. (2004) Role of truncating mutations in MME gene in fetomaternal alloimmunisation and antenatal glomerulopathies. Lancet 364(9441): 1252-1259.
7. Laurence H Beck Jr, Ramon GB Bonegio, Gérard Lambeau, David M Beck, David W Powell, et al. (2009) M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. N Engl J Med 361(1): 11-21.
8. Nicola M Tomas, Laurence H Beck Jr, Catherine Meyer-Schwesinger, Barbara Seitz-Polski, Hong Ma, et al. (2014) Thrombospondin type-1 domain-containing 7A in idiopathic membranous nephropathy. N Engl J Med 371(24): 2277-2287.
9. SHARMA SG, LARSEN CP (2018) Tissue staining for THSD7A in glomeruli correlates with serum antibodies in primary membranous nephropathy: a clinicopathological study. Mod Pathol 31(4): 616-622.
10. Sanjeev Sethi, Benjamin J Madden, Hanna Debiec, M Cristine Charlesworth, LouAnn Gross et al. (2019) Exostosin 1/Exostosin 2-Associated Membranous Nephropathy. J Am Soc Nephrol 30(6): 1123-1136.
11. Sanjeev Sethi, Hanna Debiec, Benjamin Madden, M Cristine Charlesworth, Johann Morelle, et al. (2020) Neural epidermal growth factor-like 1 protein (NELL-1) associated membranous nephropathy. Kidney Int 97(1): 163-174.
12. Tiffany N Caza, Samar I Hassen, Zeljko Dvanajscak, Michael Kuperman, Rick Edmondson, et al. (2021) NELL1 is a target antigen in malignancy-associated membranous nephropathy. Kidney Int 99(4): 967-976.
13. Sanjeev Sethi, Hanna Debiec, Benjamin Madden, Marina Vivarelli, M Cristine Charlesworth, et al. (2020) Semaphorin 3B-associated

membranous nephropathy is a distinct type of disease predominantly present in pediatric patients. Kidney Int 98(5): 1253-1264.

14. Tiffany N Caza, Samar I Hassen, Michael Kuperman, Shree G Sharma, Zeljko Dvanajscak, et al. (2021) Neural cell adhesion molecule 1 is a novel autoantigen in membranous lupus nephritis. Kidney Int 100(1): 171-181.

15. Sanjeev Sethi, Benjamin Madden, Hanna Debiec, Johann Morelle, M Cristine Charlesworth, et al. (2021) Protocadherin 7-Associated Membranous Nephropathy. J Am Soc Nephrol 32(5): 1249-1261.

16. Laith Farah Al Rabadi, Tiffany Caza, Claire Trivin Avillach, Aylin R Rodan, Nicole Andeen, et al. (2021) Serine Protease HTRA1 as a Novel Target Antigen in Primary Membranous Nephropathy. J Am Soc Nephrol 32(7): 1666-1681.

17. !!! INVALID CITATION !!! [6].

18. Maurizio Bruschi, Maria Luisa Carnevali, Corrado Murtas, Giovanni Candiano, Andrea Petretto, et al. (2011) Direct characterization of target podocyte antigens and auto-antibodies in human membranous glomerulonephritis: Alfa-enolase and borderline antigens. J Proteomics 74(10): 2008-2017.

19. Marco Prunotto, Maria Luisa Carnevali, Giovanni Candiano, Corrado Murtas, Maurizio Bruschi, et al. (2010) Autoimmunity in membranous nephropathy targets aldose reductase and SOD2. J Am Soc Nephrol 21(3): 507-519.

20. GUPTA S, PEPPER R J, ASHMAN N, WALSH SB (2018) Nephrotic Syndrome: Oedema Formation and Its Treatment With Diuretics. Front Physiol 9: 1868.

21. C Ponticelli, P Altieri, F Scolari, P Passerini, D Roccatello, et al. (1998) A randomized study comparing methylprednisolone plus chlorambucil versus methylprednisolone plus cyclophosphamide in idiopathic membranous nephropathy. J Am Soc Nephrol 9(3): 444-450.

22. Bhadran Bose, Edmund YM Chung, Regina Hong, Giovanni FM Strippoli, David W Johnson, et al. (2022) Immunosuppression therapy for idiopathic membranous nephropathy: systematic review with network meta-analysis. J Nephrol 35(4): 1159-1170.

23. LUTZ J (2021) Pathophysiology, diagnosis, and treatment of membranous nephropathy. Nephrol Ther 17S: S1-S10.

24. Ji Young Choi, Dong Ki Kim, Yang Wook Kim, Tae Hyun Yoo, Jung Pyo Lee, et al. (2018) The Effect of Mycophenolate Mofetil versus Cyclosporine as Combination Therapy with Low Dose Corticosteroids in High-risk Patients with Idiopathic Membranous Nephropathy: a Multicenter Randomized Trial. J Korean Med Sci 33(9): e74.

25. Piero Ruggenenti, Paolo Cravedi, Antonietta Chianca, Annalisa Perna, Barbara Ruggiero, et al. (2002) Rituximab for idiopathic membranous nephropathy. Lancet 360(9337): 923-924.

26. RONCO P, PLAISIER E, DEBIEC H (2021) Advances in Membranous Nephropathy. J Clin Med 10(4): 607.

27. PODESTA MA, RUGGIERO B, REMUZZI G, RUGGENENTI P (2020) Ofatumumab for multirelapsing membranous nephropathy complicated by rituximab-induced serum-sickness. BMJ Case Rep 13(1): e232896.

28. Ekkehard Mössner, Peter Brünker, Samuel Moser, Ursula Püntener, Carla Schmidt, et al. (2010) Increasing the efficacy of CD20 antibody therapy through the engineering of a new type II anti-CD20 antibody with enhanced direct and immune effector cell-mediated B-cell cytotoxicity. Blood 115(22): 4393-4402.

29. SETHI S, KUMAR S, LIM K, JORDAN SC (2020) Obinutuzumab is Effective for the Treatment of Refractory Membranous Nephropathy. Kidney Int Rep 5(9): 1515-1518.

30. Mengbing Lin, Jian Zhang, Yueling Zhang, Jiefeng Luo, Shengliang Shi (2022) Ocrelizumab for multiple sclerosis. Cochrane Database Syst Rev 5(5): CD013247.

31. SCHMIDT T, SCHULZE M, HARENDZA S, HOXHA E (2021) Successful treatment of PLA (2)R1-antibody positive membranous nephropathy with ocrelizumab. J Nephrol 34(2): 603-606.

32. Wang Mengdi, Guo Yifan, Wang Yufeng, et al. (2019) Exploration of the differentiation and treatment rules of idiopathic membranous nephropathy based on literature analysis. Global Traditional Chinese Medicine12 (12): 1834-1840.

33. Zhu Pengyu, Wang Yaoguang (2021) Summary of clinical experience of Professor Huang Wenzheng in the diagnosis and treatment of primary membranous nephropathy. Tianjin Traditional Chinese Medicine38 (2): 176-179.

34. Tang Wenli, Ma Fang, Zhan Yongli (2020) Experience in the Treatment of Idiopathic Membranous Nephropathy with Qi Tonifying, Yang Warming, Blood Activating, and Water Regulating Methods. World Traditional Chinese Medicine 15(18): 2785-2789.

35. Zhang Haitao, Ma Lei, Liu Yuning's (2013) experience in treating idiopathic membranous nephropathy. Chinese Journal of Integrated Traditional Chinese and Western Medicine Nephropathy 14 (1): 4-5.

36. Yu Dongrong Building, Zhu Bin (2000) Clinical observation on 25 cases of primary membranous nephropathy treated with integrated traditional Chinese and Western medicine. Chinese Clinical Doctor (9): 37-39.

37. Chen Yiping, Tang Liqun, Hu Zhongyi, et al. (1998) Clinical observation on the treatment of 31 cases of membranous nephritis with a series of formulas for tonifying qi and promoting blood circulation. Journal of Traditional Chinese Medicine (12): 731-808.

38. Zhang Zhengmei, Shen Zilong, Wang Meijie, et al. (2023) A master of traditional Chinese medicine, has gained experience in the treatment of idiopathic membranous nephropathy through the "Six Pairs Theory" China Medical Journal 20 (14): 155-158.

39. Meng Xi, Ding Wei, Wang Yaoguang's (2023) clinical experience in treating idiopathic membranous nephropathy. Inner Mongolia Traditional Chinese Medicine 42 (4): 81-83.